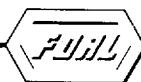


Final report - Teratologic evaluation of FDA 71-25 (Butylated Hydroxy Toluene (Ionol))  
in Mice, Rats & Hamsters 10/2/72

FOOD AND DRUG

LABORATORIES, INC.



MAURICE AVENUE AT 58TH STREET MASPETH NEW YORK 1137

FINAL

October 2, 1972

Teratologic Evaluation of FDA 71-25

(Butylated Hydroxy Toluene (Ionol))

in

Mice, Rats, and Hamsters

M I C E

**Food and Drug Research Laboratories**  
I N C O R P O R A T E D



Maurice Avenue at 58<sup>th</sup> Street  
Maspeth, New York 11378

Telephone: TWining 4-0800  
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**F I N A L  
R E P O R T**

Submitted to: DHEW/Public Health Service  
Food and Drug Administration CA-272  
5600 Fishers Lane-Room 5C-13  
Rockville, Maryland 20852

Date October 2, 1972  
Laboratory No. 0893 m  
Contract No. FDA 71-260

Sample: White crystalline material

Marking: FDA 71-25 (Butylated hydroxy toluene (Ionol))

Examination Requested: Teratologic evaluation of FDA 71-25 in mice.

Procedure: See Appendix I


Results: See Tables 1 through 4 and Appendix II

Conclusion: Subject to reexamination in the light of later findings, the following is concluded:

"The administration of up to 180 mg/kg (body weight) of the test material to pregnant mice for 10 consecutive days had no clearly discernible effect on nidation or on maternal or fetal survival. The number of abnormalities seen in either soft or skeletal tissues of the test groups did not differ from the number occurring spontaneously in the sham-treated controls."

Comment: Attention is called to the fact that this is the twelfth of a series of reports which will be issued in accordance with the terms of the contract cited above. Eventually, a total of at least 42 compounds will have been tested in 21 pairs; each pair being run concurrently against one sham-treated control and one positive control group. Because of the inherent variability of biological data of the type dealt with here, the accumulation and pooling of sequential sets of control values will greatly enhance the statistical value of the findings and the ultimate reliability of the test results.

FOOD AND DRUG RESEARCH LABORATORIES, INC.

  
Kenneth Morgareidge, Ph.D.  
Vice President

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FOOD AND DRUG RESEARCH LABORATORIES, INC.

Groups: 111 & 112; 117 through 120

Date August 31, 1972

Material: FDA 71-25

Table 1  
Fate Summary  
( Mice )

Laboratory No. 0893 m

Group	Material	Dose** mg/kg	Total		At Term	
			Mated	Pregnant	Surviving (Total)	Number Pregnant
111	Sham	0.0	22	20	22	21
112	Aspirin*	150.0	24	21	24	21
117	FDA 71-25	2.0	27	21	27	21
118	FDA 71-25	8.0	28	20	27	20
119	FDA 71-25	39.0	27	20	27	20
120	FDA 71-25	180.0	27	21	26	20

\* Positive Control

\*\* Administered as a solution in anhydrous corn oil; 1 ml per kg of body weight

**FOOD AND DRUG RESEARCH LABORATORIES, INC.**

Group: 111 & 112; 117 through 120

Date: August 31, 1971

Material: FDA 71-25

**Table 2**  
**Reproduction Data**  
( Mice )

Laboratory No.: 0893 m

Group:	111	112	117	118	119	120
Dose (mg/kg):	Sham	Aspirin*	2.0	8.0	39.0	180.0
<b>Pregnancies</b>						
Total No.	20	21	21	20	20	21
Died or Aborted (before Day 17)	0	0	0	1	0	1
To term (on Day 17)	20	21	21	20	20	20
<b>Corpora Lutea</b>						
Total No.	308	324	340	336	354	343
Average/dam mated	14.0	14.1	12.6	12.0	13.1	12.7
<b>Live Litters</b>						
Total No.*	19	21	21	20	20	20
<b>Implant Sites</b>						
Total No.	249	267	252	231	248	248
Average/dam*	12.5	12.7	12.0	11.6	12.4	12.4
<b>Resorptions</b>						
Total No.*	26	15	11	15	23	8
Dams with 1 or more sites resorbed	11	8	9	9	11	8
Dams with all sites resorbed	1	0	0	0	0	0
Per cent partial resorptions	55.0	38.1	42.9	45.0	55.0	40.0
Per cent complete resorptions	5.00	--	--	--	--	--
<b>Live Fetuses</b>						
Total No.	221	250	237	214	224	234
Average/dam*	11.1	11.9	11.3	10.7	11.2	11.7
Sex ratio (M/F)	0.76	0.84	1.01	1.14	1.02	0.77
<b>Dead Fetuses</b>						
Total No.*	2	2	4	2	1	6
Dams with 1 or more dead	2	2	4	2	1	3
Dams with all dead	0	0	0	0	0	0
Per cent partial dead	10.0	9.52	19.1	10.0	5.00	15.0
Per cent all dead	--	--	--	--	--	--
<b>Average Fetus Weight, g</b>	0.82	0.79	0.86	0.88	0.92	0.84

\*Includes only those dams examined at term.

\*\*Positive Control: 150.0 mg/kg

**FOOD AND DRUG RESEARCH LABORATORIES, INC.**

Groups 111 & 112; 117 through 120

Laboratory No. 0893 m

Table 3

Material FDA 71-25

Date August 31, 1972

**Summary of Skeletal Findings\***  
(Mice)

Findings	Group No. Dose (mg/kg)	111 Sham	112 Aspirin**	117 2.0	118 8.0	119 39.0	120 180.0
Live Fetuses Examined (at term)		155/19	173/21	167/21	150/20	150/20	165/20
Sternebrae							
Incomplete oss.		84/19	126/21	88/20	71/19	57/16	96/19
Scrambled							
Bipartite		8/5	7/7	12/9	1/1	3/3	6/5
Fused			1/1				
Extra							
Missing		35/9	40/14	29/9	12/7	12/8	28/9
Other							
Ribs							
Incomplete oss.							
Fused/split							
Wavy							
Less than 12							
More than 13		17/9	6/4	23/10	9/5	19/10	28/12
Other							
Vertebrae							
Incomplete oss.		3/3	1/1				
Scrambled							
Fused							
Extra ctrs. oss.							
Scoliosis			1/1				
Tail defects							
Other							
Skull							
Incomplete closure							
Missing							
Cranioostosis							
Other							
Extremities							
Incomplete oss.		3/3		2/2		1/1	3/2
Missing							
Extra							
Miscellaneous							
Hyoid; missing		45/13	68/19	55/17	33/12	42/14	51/15
Hyoid; reduced		18/10	22/14	21/12	10/7	23/11	17/8

\* Numerator=Number of fetuses affected; Denominator=Number of litters affected

\*\* Positive control at 150.0 mg/kg

FOOD AND DRUG RESEARCH LABORATORIES, INC.

Groups 111 & 112; 117 through 120

Date August 31, 1972

Material FDA 71-25

Laboratory No. 0893 m

Table 3-a

Summary of Soft Tissue Abnormalities  
(Mice)

Group	Material	Dose level mg/kg	Dam	Number of Pups	Description
117	FDA 71-25	2.0	M 3011	1	Meningoencephalocele
			M 3013	1	Meningoencephalocele

**FOOD AND DRUG RESEARCH LABORATORIES, INC.**

Groups 111 & 112; 117 through 120

Date August 31, 1972

Species Mice

Table 4

Laboratory No. 0893 m

Average Body Weights \*

Group	Material	Dose Level	-----Day-----				
			0	6	11	15	17**
		mg/kg	-----g-----				
111	Sham	0.0	27.0	31.0	32.1	39.5	45.8 (20)
112	Aspirin***	150.0	29.1	32.7	35.4	43.2	48.9 (21)
117	FDA 71-25	2.0	27.2	30.7	32.7	41.1	46.9 (21)
118	FDA 71-25	8.0	27.4	30.0	32.5	40.2	46.3 (20)
119	FDA 71-25	39.0	29.2	32.9	35.8	44.5	50.8 (20)
120	FDA 71-25	180.0	30.3	33.2	36.2	44.9 <sup>a</sup>	50.9 (20)

\* Of pregnant dams

\*\* Number of surviving dams in parentheses (c.f. Table 1)

\*\*\* Positive control: 150.0 mg/kg

a Average body weights of 16 dams





## Appendix I

### Teratology Study in Mice

Virgin adult female albino CD-1 outbred mice were individually housed in disposable plastic cages in temperature and humidity-controlled quarters with free access to food and fresh tap water. They were mated with young adult males, and observation of the vaginal sperm plug was considered Day 0 of gestation. Beginning on Day 6 and continuing daily through Day 15 of gestation, the females were dosed with the indicated dosages by oral intubation; the controls were sham treated.

Body weights were recorded on Days 0, 6, 11, 15, and 17 of gestation. All animals were observed daily for appearance and behavior with particular attention to food consumption and weight, in order to rule out any abnormalities which may have occurred as a result of anorexic effects in the pregnant female animal.

On Day 17 all dams were subjected to Caesarean section under surgical anesthesia, and the numbers of implantation sites, resorption sites, and live and dead fetuses were recorded. The body weights of the live pups were also recorded. The urogenital tract of each dam was examined in detail for anatomical normality.

All fetuses were examined grossly for the presence of external congenital abnormalities. One-third of the fetuses of each litter underwent detailed visceral examinations employing 10X magnification. The remaining two-thirds were cleared in potassium hydroxide (KOH), stained with alizarin red S dye and examined for skeletal defects.

**FOOD AND DRUG RESEARCH LABORATORIES, INC.**

Group 111

**Appendix II**

Date August 31, 1972

Material Sham

Reproduction Data in Mice (Individual)

Laboratory No. 0893

Dose 0.0 mg/kg

Dam No.	Fate*	Corpora Lutea	Implant Sites	Fetuses		Sex		Resorption Sites	Average Fetus Weight (g)	Remarks
				Alive	Dead	M	F			
S 3331	P	16	12	11		5	6	1	0.78	
S 3332	P	15	11	8		2	6	3	0.58	
S 3333	P	16	15	13	1	3	10	1	0.61	
S 3334	P	13	10	10		6	4		0.62	
S 3335	P	16	12	12		4	8		0.96	
S 3336	P	16	11	11		4	7		0.91	
S 3337	P	15	14	11	1	5	6	2	0.82	
S 3338	P	15	14	13		4	9	1	0.89	
S 3339	P	17	14	13		6	7	1	0.88	
S 3340	P	15	13	13		7	6		0.84	
S 3341	P	11	11					11	----	
S 3342	P	14	11	10		6	4	1	0.75	
S 3343	NP	0	0						----	
S 3344	P	11	10	10		5	5		0.83	
S 3345	NP	11	0						----	
S 3346	P	14	14	14		8	6		0.81	
S 3347	P	15	12	11		6	5	1	0.87	
S 3348	P	14	12	10		7	3	2	0.85	
S 3349	P	14	11	9		3	6	2	0.91	
S 3350	P	21	16	16		4	12		0.73	
S 3351	P	13	13	13		5	8		0.85	
S 3352	P	16	13	13		5	8		1.00	

\* P = Pregnant; NP = Not Pregnant

FOOD AND DRUG RESEARCH LABORATORIES, INC.

Group 112

Appendix II

Date August 31, 1972

Material Aspirin

Reproduction Data in Mice (Individual)

Laboratory No. 0893

Dose 150.0 mg/kg

Dam No.	Fate*	Corpora Lutea	Implant Sites	Fetuses		Sex		Resorption Sites	Average Fetus Weight (g)	Remarks
				Alive	Dead	M	F			
A 3331	P	16	13	12		7	5	1	0.79	
A 3332	P	14	11	9		4	5	2	0.76	
A 3333	P	15	14	14		5	9		0.74	
A 3334	P	16	11	11		4	7		0.66	
A 3335	P	20	14	11		6	5	3	0.70	
A 3336	P	18	13	12		6	6	1	0.74	
A 3337	NP	3	0						----	
A 3338	P	16	15	15		4	11		0.75	
A 3339	NP	13	0						----	
A 3340	P	-- <sup>a</sup>	16	15		7	8	1	0.69	
A 3341	P	16	15	15		5	10		0.83	
A 3342	P	12	11	11		6	5		0.89	
A 3343	P	16	13	12	1	4	8		0.73	
A 3344	P	14	12	11		6	5	1	0.74	
A 3345	P	15	12	12		6	6		0.85	
A 3346	P	14	13	12		6	6	1	0.88	
A 3347	P	11	8	8		5	3		0.78	
A 3348	P	15	13	13		9	4		0.81	
A 3349	P	15	16	13	1	8	5	2	0.84	
A 3350	P	14	10	9		1	8	1	0.78	
A 3351	NP	6	0						----	
A 3352	P	17	16	14		4	10	2	0.78	
A 3353	P	14	13	13		9	4		1.05	
A 3354	P	14	8	8		2	6		0.77	

\* P = Pregnant; NP = Not Pregnant

<sup>a</sup> Ovaries missing

FOOD AND DRUG RESEARCH LABORATORIES, INC.

Group 117

Appendix II

Date August 31, 1972

Material FDA 71-25

Reproduction Data in Mice (Individual)

Laboratory No. 0893 m

Dose 2.0 mg/kg

Dam No.	Fate*	Corpora Lutea	Implant Sites	Fetuses		Sex		Resorption Sites	Average Fetus Weight (g)	Remarks
				Alive	Dead	M	F			
M 3001	NP	1	0						----	
M 3002	P	13	12	10	1	4	6	1	0.72	
M 3003	P	13	14	13	1	7	6		0.74	
M 3004	P	16	13	13		7	6		0.85	
M 3005	NP	0	0						----	
M 3006	P	16	11	10		6	4	1	0.83	
M 3007	P	13	12	12		8	4		0.79	
M 3008	NP	8	0						----	
M 3009	P	18	15	14		8	6	1	0.91	
M 3010	NP	5	0						----	
M 3011	P	14	11	8	1	4	4	2	0.87	
M 3012	P	16	14	14		4	10		0.67	
M 3013	P	13	12	10	1	3	7	1	0.78	
M 3014	NP	12	0						----	
M 3015	P	16	13	13		6	7		0.77	
M 3016	P	13	13	13		7	6		0.94	
M 3017	P	15	14	13		9	4	1	0.91	
M 3018	P	14	10	10		8	2		1.01	
M 3019	P	12	12	10		6	4	2	0.96	
M 3020	NP	11	0						----	
M 3021	P	13	12	11		3	8	1	0.86	
M 3022	P	14	12	11		5	6	1	0.87	
M 3023	P	16	12	12		5	7		0.92	
M 3024	P	15	12	12		7	5		0.92	
M 3025	P	11	7	7		2	5		1.05	
M 3026	P	16	10	10		6	4		0.86	
M 3027	P	16	11	11		4	7		0.85	

\* P = Pregnant; NP = Not Pregnant

FOOD AND DRUG RESEARCH LABORATORIES, INC.

Group 118

Appendix II

Date August 31, 1972

Material FDA 71-25

Reproduction Data in Mice (Individual)

Laboratory No. 0893 m

Dose 8.0 mg/kg

Dam No.	Fate*	Corpora Lutea	Implant Sites	Fetuses		Sex		Resorption Sites	Average Fetus Weight (g)	Remarks
				Alive	Dead	M	F			
M 3031	P	12	12	9		4	5	3	0.80	
M 3032	P	15	11	11		6	5		1.00	
M 3033	NP	4	0						----	
M 3034	NP	5	0						----	
M 3035	P	15	11	9		6	3	2	0.83	
M 3036	P	13	11	11		6	5		0.95	
M 3037	P	12	11	10		6	4	1	0.79	
M 3038	P	11	11	9		5	4	2	0.79	
M 3039	P	12	12	12		8	4		0.91	
M 3040	NP	5	0						----	
M 3041	P	12	10	10		3	7		0.93	
M 3042	P	16	14	14		10	4		0.82	
M 3043	P	15	11	11		6	5		0.94	
M 3044	P	9	6	5		3	2	1	0.94	
M 3045	P	14	13	13		6	7		0.82	
M 3046	P	14	12	12		7	5		0.98	
M 3047	P	16	13	13		6	7		0.87	
M 3048	P	17	12	12		5	7		0.89	
M 3049	NP	8	0						----	
M 3050	P	13	9	8		6	2	1	0.81	
M 3051	P	16	12	11		6	5	1	0.78	
M 3052	NP		0						----	Died Day 15
M 3053	NP	3	0						----	
M 3054	P	19	13	10		3	7	3	1.02	
M 3055	NP	11	0						----	
M 3056	NP	13	0						----	
M 3057	P	19	12	11	1	7	4		0.91	
M 3058	P	17	15	13	1	5	8	1	0.76	

\* P = Pregnant; NP = Not Pregnant

FOOD AND DRUG RESEARCH LABORATORIES, INC.

Group 119

Appendix II

Date August 31, 1972

Material FDA 71-25

Reproduction Data in Mice (Individual)

Laboratory No. 0893 m

Dose 39.0 mg/kg

Dam No.	Fate*	Corpora Lutea	Implant Sites	Fetuses		Sex		Resorption Sites	Average Fetus Weight (g)	Remarks
				Alive	Dead	M	F			
M 3061	P	14	9	9		5	4		0.86	
M 3062	NP	4	0						----	
M 3063	P	18	15	14	1	7	7		0.84	
M 3064	NP	7	0						----	
M 3065	P	13	11	11		8	3		0.92	
M 3066	P	11	9	7		4	3	2	0.69	
M 3067	P	13	12	11		8	3	1	0.84	
M 3068	P	13	12	12		4	8		0.85	
M 3069	P	13	13	11		7	4	2	0.93	
M 3070	P	18	15	11		3	8	4	0.87	
M 3071	P	15	3	3		2	1		1.01	
M 3072	P	15	12	11		6	5	1	0.96	
M 3073	P	17	14	13		7	6	1	0.82	
M 3074	P	14	10	10		4	6		1.08	
M 3075	P	19	18	13		6	7	5	0.94	
M 3076	P	14	13	13		5	8		0.91	
M 3077	P	13	12	11		7	4	1	1.27	
M 3078	NP	10	0						----	
M 3079	NP	9	0						----	
M 3080	NP	5	0						----	
M 3081	NP	8	0						----	
M 3082	P	15	14	12		5	7	2	0.84	
M 3083	NP	5	0						----	
M 3084	P	19	13	12		6	6	1	0.85	
M 3085	P	18	14	14		10	4		1.22	
M 3086	P	16	15	12		3	9	3	0.85	
M 3087	P	18	14	14		6	8		0.94	

\* P = Pregnant; NP = Not Pregnant

FOOD AND DRUG RESEARCH LABORATORIES, INC.

Group 120

Appendix II

Date August 31, 1972

Material FDA 71-25

Reproduction Data in Mice (Individual)

Laboratory No. 0893 m

Dose 180.0 mg/kg

Dam No.	Fate*	Corpora Lutea	Implant Sites	Fetuses		Sex		Resorption Sites	Average Fetus Weight (g)	Remarks
				Alive	Dead	M	F			
M 3091	P	13	14	14		8	6		0.89	
M 3092	P	20	14	13		5	8	1	0.94	
M 3093	P	23	15	15		9	6		0.62	
M 3094	NP	3	0						----	
M 3095	P	12	11	11		3	8		0.74	
M 3096	NP	5	0						----	
M 3097	P	14	12	11		4	7	1	0.87	
M 3098	P	15	14	13		9	4	1	0.93	
M 3099	P	15	12	11		5	6	1	0.84	
M 3100	P	15	14	14		7	7		1.07	
M 3101	P	13	12	9	3	3	6		0.72	
M 3102	P	14	12	12		6	6		0.79	
M 3103	P	13	13	11	1	5	6	1	0.78	
M 3104	P	12	11	10		3	7	1	1.00	
M 3105	P	16	11	11		5	6		0.85	
M 3106	P	10	7	7		4	3		1.00	
M 3107	P	17	14	14		4	10		0.88	
M 3108	P	18	14	14		4	10		0.77	
M 3109	P	17	13	12		6	6	1	0.85	
M 3110	P	13	10	10		5	5		0.81	
M 3111	NP	7	0						----	
M 3112	NP	5	0						----	
M 3113	NP	3	0						----	
M 3114	NP	7	0						----	
M 3115	P	10	9					9	-----	Died Day 12
M 3116	P	18	13	11	2	2	9		0.64	
M 3117	P	15	12	11		5	6	1	0.82	

\* P = Pregnant; NP = Not Pregnant

R A T S



**Food and Drug Research Laboratories**  
I N C O R P O R A T E D



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**F I N A L  
R E P O R T**

Submitted to: DHEW/Public Health Service  
Food and Drug Administration CA-272  
5600 Fishers Lane-Room 5C-13  
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Date October 2, 1972  
  
Laboratory No. 0894 m  
Contract No. FDA 71-260

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Marking: FDA 71-25 (Butylated hydroxy toluene (Ionol))

Examination Requested: Teratologic evaluation of FDA 71-25 in rats

Procedure: See Appendix I

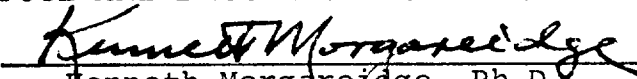
Results: See Tables 1 through 4 and Appendix II

Conclusion: Subject to reexamination in the light of later findings, the following is concluded:

"The administration of up to 225 mg/kg (body weight) of the test material to pregnant rats for 10 consecutive days had no clearly discernible effect on nidation or on maternal or fetal survival. The number of abnormalities seen in either soft or skeletal tissues of the test groups did not differ from the number occurring spontaneously in the sham-treated controls."

Comment: Attention is called to the fact that this is the twelfth of a series of reports which will be issued in accordance with the terms of the contract cited above. Eventually, a total of at least 42 compounds will have been tested in 21 pairs; each pair being run concurrently against one sham-treated control and one positive control group. Because of the inherent variability of biological data of the type dealt with here, the accumulation and pooling of sequential sets of control values will greatly enhance the statistical value of the findings and the ultimate reliability of the test results.

FOOD AND DRUG RESEARCH LABORATORIES, INC.

  
Kenneth Morgareidge, Ph.D.  
Vice President

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FOOD AND DRUG RESEARCH LABORATORIES, INC.

Groups: 111 & 112; 117 through 120

Date August 31, 1972

Material: FDA 71-25

Table 1

Laboratory No. 0894 m

Fate Summary  
( Rats )

Group	Material	Dose ** mg/kg	Total		At Term	
			Mated	Pregnant	Surviving (Total)	Number Pregnant
111	Sham	0.0	24	24	24	24
112	Aspirin*	250.0	24	22	23	22
117	FDA 71-25	2.0	24	24	24	24
118	FDA 71-25	10.0	24	24	24	24
119	FDA 71-25	48.0	24	23	24	23
120	FDA 71-25	225.0	24	24	23	23

\* Positive Control

\*\* Administered as a solution in anhydrous corn oil; 1 ml per kg of body weight

**FOOD AND DRUG RESEARCH LABORATORIES, INC.**

Group: 111 & 112; 117 through 120

Date: August 31, 1972

Material: FDA 71-25

**Table 2**  
**Reproduction Data**  
( Rats )

Laboratory No.: 0894 m

Group:	111	112	117	118	119	120
Dose (mg/kg):	Sham	Aspirin**	2.0	10.0	48.0	225.0
<b>Pregnancies</b>						
Total No.	24	22	24	24	23	24
Died or Aborted (before Day 20)	0	1	0	0	0	1
To term (on Day 20)	24	22	24	24	23	23
<b>Corpora Lutea</b>						
Total No.	272	256	274	260	243	248
Average/dam mated	11.3	11.6	11.4	10.8	10.1	10.3
<b>Live Litters</b>						
Total No.*	23	21	24	24	23	23
<b>Implant Sites</b>						
Total No.	254	237	270	254	235	240
Average/dam*	10.6	10.8	11.3	10.6	10.2	10.4
<b>Resorptions</b>						
Total No.*	2	31	8	9	11	10
Dams with 1 or more sites resorbed	1	11	4	8	8	5
Dams with all sites resorbed	0	1	0	0	0	0
Per cent partial resorptions	4.17	50.0	16.7	33.3	34.8	21.7
Per cent complete resorptions	--	4.55	--	--	--	--
<b>Live Fetuses</b>						
Total No.	252	204	262	245	224	230
Average/dam*	10.5	9.27	10.9	10.2	9.74	10.0
Sex ratio (M/F)	0.92	0.86	0.82	1.13	0.90	0.89
<b>Dead Fetuses</b>						
Total No.*	0	2	0	0	0	0
Dams with 1 or more dead	--	2	--	--	--	--
Dams with all dead	--	0	--	--	--	--
Per cent partial dead	--	9.09	--	--	--	--
Per cent all dead	--	--	--	--	--	--
<b>Average Fetus Weight, g</b>	3.74	2.64	3.88	3.80	3.92	3.87

\*Includes only those dams examined at term.

\*\*Positive Control: 250.0 mg/kg

**FOOD AND DRUG RESEARCH LABORATORIES, INC.**

Groups 111 & 112; 117 through 120

Laboratory No. 0894 m

Table 3

Material FDA 71-25

Date August 31, 1972

**Summary of Skeletal Findings \***  
(Rats)

Findings	Group No. Dose (mg/kg)	111 Sham	112 Aspirin**	117 2.0	118 10.0	119 48.0	120 225.0
Live Fetuses Examined (at term)		171/24	136/21	175/24	166/24	148/23	153/23
Sternebrae							
Incomplete oss.		19/14	118/21	11/9	11/8	8/6	9/6
Scrambled							
Bipartite			5/5				
Fused							
Extra							
Missing		1/1	74/20				
Other							
Ribs							
Incomplete oss.			27/11				
Fused/split			7/6				
Wavy		18/7	48/13	4/4	5/4	9/6	2/1
Less than 12			1/1				
More than 13			69/19				
Other							
Vertebrae							
Incomplete oss.		2/2	106/21		4/4	3/3	
Scrambled							
Fused			2/1				
Extra ctrs. oss.							
Scoliosis			12/5				
Tail defects							
Other							
Skull							
Incomplete closure		26/10	95/21	16/12	21/7	24/12	6/6
Missing							
Cranioostosis							
Other							
Extremities							
Incomplete oss.			9/5				
Missing							
Extra							
Miscellaneous							
Hyoid; missing		14/9	86/19	13/8	16/6	17/9	14/7
Hyoid; reduced		2/2	3/3	5/5	8/4	1/1	2/2

\* Numerator=Number of fetuses affected; Denominator=Number of litters affected  
 \*\* Positive control at 250.0 mg/kg

**FOOD AND DRUG RESEARCH LABORATORIES, INC.**

**Groups** 111 & 112; 117 through 120

**Date** August 31, 1972

**Material** FDA 71-25

**Laboratory No.** 0894 m

**Table 3-a**  
**Summary of Soft Tissue Abnormalities**  
**(Rats)**

Group	Material	Dose level mg/kg	Dam	Number of Pups	Description
112	Aspirin*	250.0	A 4338	1	Exencephaly, spina bifida, entero- hepatocoele
			A 4339	2 1	Exencephaly, Spina bifida
			A 4347	3 2	Exencephaly Spina bifida
			A 4399	1	Exencephaly
			A 4352	2	Exencephaly
			A 4353	1	Exencephaly, spina bifida, entero- hepatocoele

\* Positive control at 250.0 mg/kg

FOOD AND DRUG RESEARCH LABORATORIES, INC.

Groups 111 & 112; 117 through 120

Date August 31, 1972

Species Rats

Table 4

Laboratory No. 0894 m

Average Body Weights\*

Group	Material	Dose Level mg/kg	Day-----				
			0	6	11	15	20**
111	Sham	0.0	217	235	253	277	343 (24)
112	Aspirin***	250.0	219	238	256	277	331 (22)
117	FDA 71-25	2.0	217	233	255	280	347 (24)
118	FDA 71-25	10.0	214	234	255	275	341 (24)
119	FDA 71-25	48.0	213	231	251	275	341 (23)
120	FDA 71-25	225.0	208	227	243	264	332 (23)

\* Of pregnant dams

\*\* Number of surviving dams in parentheses (c.f. Table 1)

\*\*\* Positive control:



## Appendix I

### Teratology Study in Rats

Virgin adult female albino rats (Wistar derived stock) were individually housed in mesh bottom cages in temperature and humidity-controlled quarters with free access to food and fresh tap water. They were mated with young adult males, and observation of the vaginal sperm plug was considered Day 0 of gestation. Beginning on Day 6 and continuing daily through Day 15 of gestation, the females were dosed with the indicated dosages by oral intubation; the controls were sham treated.

Body weights were recorded on Days 0, 6, 11, 15, and 20 of gestation. All animals were observed daily for appearance and behavior with particular attention to food consumption and weight, in order to rule out any abnormalities which may have occurred as a result of anorexic effects in the pregnant female animal.

On Day 20 all dams were subjected to Caesarean section under surgical anesthesia, and the numbers of implantation sites, resorption sites, and live and dead fetuses were recorded. The body weights of the live pups were also recorded. The urogenital tract of each dam was examined in detail for anatomical normality.

All fetuses were examined grossly for the presence of external congenital abnormalities. One-third of the fetuses of each litter underwent detailed visceral examinations employing 10X magnification. The remaining two-thirds were cleared in potassium hydroxide (KOH), stained with alizarin red S dye and examined for skeletal defects.

FOOD AND DRUG RESEARCH LABORATORIES, INC.

Group 111

Appendix II

Date August 31, 1972

Material Sham

Reproduction Data in Rats (Individual)

Laboratory No. 0894

Dose 0.0 mg/kg

Dam No.	Fate*	Corpora Lutea	Implant Sites	Fetuses		Sex		Resorption Sites	Average Fetus Weight (g)	Remarks
				Alive	Dead	M	F			
S 4331	P	11	11	11		5	6		3.29	
S 4332	P	10	9	9		6	3		5.16	
S 4333	P	9	9	9		2	7		4.28	
S 4334	P	11	10	10		4	6		3.86	
S 4335	P	13	13	13		5	8		3.66	
S 4336	P	13	13	13		7	6		3.25	
S 4337	P	9	1	1		0	1		4.20	
S 4338	P	13	13	13		5	8		4.19	
S 4339	P	11	11	11		4	7		3.70	
S 4340	P	11	11	11		7	4		3.62	
S 4341	P	9	9	7		6	1	2	3.97	
S 4342	P	13	13	13		7	6		3.78	
S 4343	P	13	13	13		7	6		3.75	
S 4344	P	10	10	10		8	2		3.64	
S 4345	P	13	13	13		3	10		3.82	
S 4346	P	10	7	7		6	1		3.87	
S 4347	P	13	13	13		4	9		3.58	
S 4348	P	12	7	7		2	5		3.53	
S 4349	P	12	12	12		4	8		3.47	
S 4350	P	10	10	10		5	5		3.72	
S 4351	P	12	12	12		6	6		3.72	
S 4352	P	9	9	9		6	3		4.01	
S 4353	P	13	13	13		6	7		3.23	
S 4354	P	12	12	12		6	6		3.62	

\* P = Pregnant; NP = Not Pregnant



FOOD AND DRUG RESEARCH LABORATORIES, INC.

Group 112

Appendix II

Date August 31, 1972

Material Aspirin

Reproduction Data in Rats (Individual)

Laboratory No. 0894

Dose 250.0 mg/kg

Dam No.	Fate*	Corpora Lutea	Implant Sites	Fetuses		Sex		Resorption Sites	Average Fetus Weight (g)	Remarks
				Alive	Dead	M	F			
A 4331	P	8	5					5	----	
A 4332	P	12	8	7		1	6	1	4.06	
A 4333	P	8	8	8		1	7		3.11	
A 4334	P	13	13	12	1	10	3		3.14	
A 4335	P	11	11	7		3	4	4	2.83	
A 4336	P	9	9	7		3	4	2	2.86	
A 4337	P	9	9	9		4	5		2.99	
A 4338	P	17	9	6	1	3	3	2	2.58	
A 4339	P	8	8	8		4	4		2.25	
A 4340	P	16	16	16		10	6		2.88	
A 4341	P	12	12	12		5	7		2.23	
A 4342	P	11	12	11		5	6	1	2.73	
A 4343	P	15	12	12		6	6		2.79	
A 4344	P	14	14	14		4	10		2.26	
A 4245	P	12	12	12		5	7		2.18	
A 4346	P	10	10	7		2	5	3	2.70	
A 4347	P	9	9	7		3	4	2	2.19	
A 4348	P	11	10	9		5	4	1	2.83	
A 4349	P	13	13	13		8	5		2.65	
A 4350	NP	0	0						----	Died Day 8
A 4351	NP	0	0						----	
A 4352	P	11	11	9		5	4	2	1.83	
A 4353	P	14	13	5		3	2	8	1.78	
A 4354	P	13	13	13		5	8		2.74	

\* P = Pregnant; NP = Not Pregnant

FOOD AND DRUG RESEARCH LABORATORIES, INC.

Group 117

Appendix II

Date August 31, 1972

Material FDA 71-25

Reproduction Data in Rats (Individual)

Laboratory No. 0894 m

Dose 2.0 mg/kg

Dam No.	Fate*	Corpora Lutea	Implant Sites	Fetuses		Sex		Resorption Sites	Average Fetus Weight (g)	Remarks
				Alive	Dead	M	F			
M 4001	P	11	11	11		5	6		3.99	
M 4002	P	12	12	12		6	6		3.73	
M 4003	P	10	10	8		4	4	2	4.13	
M 4004	P	13	13	13		6	7		3.92	
M 4005	P	13	13	13		5	8		3.71	
M 4006	P	11	11	11		3	8		4.02	
M 4007	P	13	13	13		9	4		3.84	
M 4008	P	11	11	11		3	8		3.89	
M 4009	P	9	9	9		5	4		4.51	
M 4010	P	13	13	13		4	9		3.45	
M 4011	P	13	13	13		5	8		4.09	
M 4012	P	10	10	10		5	5		3.95	
M 4013	P	15	15	13		3	10	2	3.91	
M 4014	P	11	11	11		5	6		3.43	
M 4015	P	11	11	11		5	6		4.08	
M 4016	P	11	7	7		3	4		3.24	
M 4017	P	10	10	10		3	7		3.95	
M 4018	P	9	9	9		6	3		4.06	
M 4019	P	12	12	11		3	8	1	4.14	
M 4020	P	12	12	9		6	3	3	3.74	
M 4021	P	11	11	11		5	6		3.99	
M 4022	P	11	11	11		4	7		3.57	
M 4023	P	11	11	11		6	5		4.00	
M 4024	P	11	11	11		9	2		4.08	

\* P = Pregnant; NP = Not Pregnant

FOOD AND DRUG RESEARCH LABORATORIES, INC.

Group 118

Appendix II

Date August 31, 1972

Material FDA 71-25

Reproduction Data in Rats (Individual)

Laboratory No. 0894 m

Dose 10.0 mg/kg

Dam No.	Fate*	Corpora Lutea	Implant Sites	Fetuses		Sex		Resorption Sites	Average Fetus Weight (g)	Remarks
				Alive	Dead	M	F			
M 4031	P	11	11	10		4	6	1	3.94	
M 4032	P	9	9	9		6	3		3.77	
M 4033	P	9	9	9		4	5		4.81	
M 4034	P	11	11	11		4	7		3.46	
M 4035	P	8	8	7		1	6	1	4.00	
M 4036	P	12	12	12		6	6		3.71	
M 4037	P	13	13	13		8	5		3.60	
M 4038	P	12	12	12		6	6		3.58	
M 4039	P	9	9	9		3	6		4.18	
M 4040	P	10	11	10		7	3	1	4.04	
M 4041	P	11	11	10		5	5	1	3.60	
M 4042	P	12	12	12		6	6		3.93	
M 4043	P	12	12	12		7	5		3.48	
M 4044	P	8	1	1		1	0		3.90	
M 4045	P	12	12	12		7	5		3.56	
M 4046	P	11	11	11		5	6		3.67	
M 4047	P	14	14	14		12	2		3.73	
M 4048	P	12	12	12		4	8		3.86	
M 4049	P	12	12	11		5	6	1	4.02	
M 4050	P	11	11	10		3	7	1	3.66	
M 4051	P	10	10	10		6	4		3.78	
M 4052	P	12	12	12		9	3		4.14	
M 4053	P	11	11	10		4	6	1	3.69	
M 4054	P	8	8	6		3	3	2	3.22	

\* P = Pregnant; NP = Not Pregnant

**FOOD AND DRUG RESEARCH LABORATORIES, INC.**

**Group** 119

**Appendix II**

**Date** August 31, 1972

**Material** FDA 71-25

**Reproduction Data in Rats (Individual)**

**Laboratory No.** 0894 m

**Dose** 48.0 mg/kg

Dam No.	Fate*	Corpora Lutea	Implant Sites	Fetuses		Sex		Resorption Sites	Average Fetus Weight (g)	Remarks
				Alive	Dead	M	F			
M 4061	P	10	10	10		4	6		4.30	
M 4062	P	9	9	9		4	5		4.03	
M 4063	P	10	4	4		3	1		4.10	
M 4064	P	12	12	10		9	1	2	3.82	
M 4065	P	12	12	10		6	4	2	3.90	
M 4066	P	11	11	11		6	5		3.94	
M 4067	P	5	5	5		1	4		4.04	
M 4068	P	10	10	10		7	3		3.55	
M 4069	P	11	9	8		3	5	1	4.19	
M 4070	P	8	8	8		3	5		4.36	
M 4071	P	5	5	5		3	2		3.90	
M 4072	P	11	11	11		1	10		3.75	
M 4073	P	14	14	14		3	11		3.74	
M 4074	P	13	13	12		4	8	1	4.73	
M 4075	NP	0	0						----	
M 4076	P	10	10	10		7	3		3.58	
M 4077	P	13	13	13		7	6		3.22	
M 4078	P	13	13	12		5	7	1	3.94	
M 4079	P	10	10	8		6	2	2	4.48	
M 4080	P	9	9	8		7	1	1	4.00	
M 4081	P	12	12	12		5	7		3.94	
M 4082	P	11	11	11		4	7		3.98	
M 4083	P	13	13	12		4	8	1	3.77	
M 4084	P	11	11	11		5	6		3.58	

\* P = Pregnant; NP = Not Pregnant

FOOD AND DRUG RESEARCH LABORATORIES, INC.

Group 120

Appendix II

Date August 31, 1972

Material FDA 71-25

Reproduction Data in Rats (Individual)

Laboratory No. 0894 m

Dose 225.0 mg/kg

Dam No.	Fate*	Corpora Lutea	Implant Sites	Fetuses		Sex		Resorption Sites	Average Fetus Weight (g)	Remarks
				Alive	Dead	M	F			
M 4091	P	12	12	12		6	6		3.90	
M 4092	P	9	1	1		1	0		5.70	
M 4093	P	13	13	13		8	5		4.95	
M 4094	P	12	12	9		5	4	3	3.66	
M 4095	P	8	8	4		4	0	4	3.75	
M 4096	P	11	11	11		2	9		3.56	
M 4097	P	12	12	11		3	8	1	3.54	
M 4098	P	10	10	10		7	3		4.02	
M 4099	P	10	10	9		2	7	1	3.79	
M 4100	P	11	11	11		4	7		3.69	
M 4101	P	12	12	12		9	3		4.03	
M 4102	P	11	11	10		5	5	1	4.01	
M 4103	P	8	8	8		4	4		3.73	
M 4104	P	10	10	10		--	--		----	Sacrificed Day 14
M 4105	P	10	10	10		6	4		3.76	
M 4106	P	11	11	11		4	7		3.42	
M 4107	P	8	8	8		4	4		3.73	
M 4108	P	12	12	12		9	3		3.83	
M 4109	P	10	10	10		4	6		3.65	
M 4110	P	11	11	11		5	6		4.12	
M 4111	P	15	15	15		2	13		3.77	
M 4112	P	11	11	11		3	8		4.17	
M 4113	P	10	10	10		5	5		3.75	
M 4114	P	11	11	11		6	5		4.75	

\* P = Pregnant; NP = Not Pregnant

HAMSTERS

**Food and Drug Research Laboratories**  
I N C O R P O R A T E D



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Maspeth, New York 11378  
Telephone: TWining 4-0800  
Cable: Foodlabs, New York

**F I N A L  
R E P O R T**

Submitted to: DHEW/Public Health Service  
Food and Drug Administration CA-272  
5600 Fishers Lane-Room 5C-13  
Rockville, Maryland 20852

Date October 2, 1972

Laboratory No. 0895 m  
Contract No. FDA 71-260

Sample: White crystalline material

Marking: FDA 71-25 (Butylated hydroxy toluene (Ionol))

Examination Requested: Teratologic evaluation of FDA 71-25 in hamsters

Procedure: See Appendix I

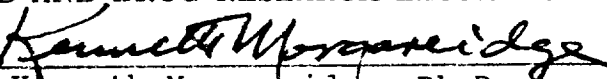
Results: See Tables 1 through 4 and Appendix II

Conclusion: Subject to reexamination in the light of later findings, the following is concluded:

"The administration of up to 280 mg/kg (body weight) of the test material to pregnant hamsters for 5 consecutive days had no clearly discernible effect on nidation or on maternal or fetal survival. The number of abnormalities seen in either soft or skeletal tissues of the test groups did not differ from the number occurring spontaneously in the sham-treated controls."

Comment: Attention is called to the fact that this is the twelfth of a series of reports which will be issued in accordance with the terms of the contract cited above. Eventually, a total of at least 42 compounds will have been tested in 21 pairs; each pair being run concurrently against one sham-treated control and one positive control group. Because of the inherent variability of biological data of the type dealt with here, the accumulation and pooling of sequential sets of control values will greatly enhance the statistical value of the findings and the ultimate reliability of the test results.

FOOD AND DRUG RESEARCH LABORATORIES, INC.

  
Kenneth Morganeidge, Ph.D.  
Vice President

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**Food and Drug Research Laboratories**  
I N C O R P O R A T E D



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**F I N A L  
R E P O R T**

Submitted to: DHEW/Public Health Service  
Food and Drug Administration CA-272  
5600 Fishers Lane-Room 5C-13  
Rockville, Maryland 20852

Date October 2, 1972

Laboratory No. 0895 m  
Contract No. FDA 71-260

Sample: White crystalline material

Marking: FDA 71-25 (Butylated hydroxy toluene (Ionol))

Examination Requested: Teratologic evaluation of FDA 71-25 in hamsters

Procedure: See Appendix I


Results: See Tables 1 through 4 and Appendix II

Conclusion: Subject to reexamination in the light of later findings, the following is concluded:

"The administration of up to 280 mg/kg (body weight) of the test material to pregnant hamsters for 5 consecutive days had no clearly discernible effect on nidation or on maternal or fetal survival. The number of abnormalities seen in either soft or skeletal tissues of the test groups did not differ from the number occurring spontaneously in the sham-treated controls."

Comment: Attention is called to the fact that this is the twelfth of a series of reports which will be issued in accordance with the terms of the contract cited above. Eventually, a total of at least 42 compounds will have been tested in 18 pairs; each pair being run concurrently against one sham-treated control and one positive control group. Because of the inherent variability of biological data of the type dealt with here, the accumulation and pooling of sequential sets of control values will greatly enhance the statistical value of the findings and the ultimate reliability of the test results.

FOOD AND DRUG RESEARCH LABORATORIES, INC.

  
Kenneth Morganeidge, Ph.D.  
Vice President

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FOOD AND DRUG RESEARCH LABORATORIES, INC.

Groups: 111 & 112; 117 through 120

Date August 31, 1972

Material: FDA 71-25

Table 1

Laboratory No. 0895 m

Fate Summary  
(Hamsters)

Group	Material	Dose ** mg/kg	Total		At Term	
			Mated	Pregnant	Surviving (Total)	Number Pregnant
111	Sham	0.0	24	21	23	20
112	Aspirin*	250.0	22	21	22	21
117	FDA 71-25	3.0	25	22	25	22
118	FDA 71-25	13.0	22	22	22	22
119	FDA 71-25	60.0	25	21	25	21
120	FDA 71-25	280.0	22	21	22	21

\* Positive Control

\*\* Administered as a solution in anhydrous corn oil; 1 ml per kg of body weight

**FOOD AND DRUG RESEARCH LABORATORIES, INC.**

Group: 111 & 112; 117 through 120

Date: August 31, 19, \_

Material: FDA 71-25

**Table 2**  
**Reproduction Data**  
**( Hamsters )**

Laboratory No.: 0895 m

Group:	111	112	117	118	119	120
Dose (mg/kg):	Sham	Aspirin**	3.0	13.0	60.0	280.0
<b>Pregnancies</b>						
Total No.	21	21	22	22	21	21
Died or Aborted (before Day 14)	1	0	0	0	0	0
To term (on Day 14)	20	21	22	22	21	21
<b>Corpora Lutea</b>						
Total No.	318	330	364	343	355	328
Average/dam mated	13.3	15.0	14.6	15.6	14.2	14.9
<b>Live Litters</b>						
Total No.*	19	21	22	22	20	21
<b>Implant Sites</b>						
Total No.	240	257	280	269	245	250
Average/dam*	12.0	12.2	12.7	12.2	11.7	11.9
<b>Resorptions</b>						
Total No.*	8	12	16	18	27	26
Dams with 1 or more sites resorbed	8	3	10	15	10	11
Dams with all sites resorbed	0	0	0	0	0	0
Per cent partial resorptions	40.0	14.3	45.5	68.2	47.6	52.4
Per cent complete resorptions	--	--	--	--	--	--
<b>Live Fetuses</b>						
Total No.	214	243	263	251	211	223
Average/dam*	10.7	11.6	12.0	11.4	10.0	10.6
Sex ratio (M/F)	0.44	0.48	0.62	0.64	0.78	0.73
<b>Dead Fetuses</b>						
Total No.*	18	2	1	0	7	1
Dams with 1 or more dead	3	2	1	--	2	1
Dams with all dead	1	0	0	--	0	0
Per cent partial dead	15.0	9.52	4.55	--	9.52	4.76
Per cent all dead	5.0	--	--	--	--	--
<b>Average Fetus Weight, g</b>	1.69	1.66	1.81	1.78	1.78	1.82

\*Includes only those dams examined at term.

\*\*Positive Control: 250.0 mg/kg

**FOOD AND DRUG RESEARCH LABORATORIES, INC.**

Groups 111 & 112; 117 through 120

Laboratory No. 0895 m

Table 3

Material FDA 71-25

Date August 31, 1972

**Summary of Skeletal Findings\***  
(Hamsters)

Findings	Group No. Dose (mg/kg)	111 Sham	112 Aspirin**	117 3.0	118 13.0	119 60.0	120 280.0
Live Fetuses Examined (at term)		148/19	169/21	184/22	170/22	151/20	152/21
Sternebrae							
Incomplete oss.		98/19	121/20	101/22	96/21	88/20	51/17
Scrambled							
Bipartite		14/8	21/11	22/14	18/12	17/10	17/11
Fused							
Extra				1/1	7/3	5/5	1/1
Missing			50/17	21/11	37/17	31/11	28/13
Other							
Ribs							
Incomplete oss.							
Fused/split							
Wavy							
Less than 12							
More than 13		42/15	41/17	22/12	21/12	33/11	15/8
Other							
Vertebrae							
Incomplete oss.							
Scrambled							
Fused							
Extra ctrs. oss.							
Scoliosis							
Tail defects							
Other							
Skull							
Incomplete closure							
Missing							
Craniostosis							
Other							
Extremities							
Incomplete oss.			2/2			4/3	
Missing							
Extra							
Miscellaneous							
Hyoid; missing			3/3			4/3	
Hyoid; reduced				1/1		3/3	

\* Numerator=Number of fetuses affected; Denominator=Number of litters affected  
 \*\* Positive control at 250.0 mg/kg

**FOOD AND DRUG RESEARCH LABORATORIES, INC.**

**Groups** 111 & 112; 117 through 120

**Date** August 31, 1972

**Material** FDA 71-25

**Laboratory No.** 0895 m

**Table 3-a**  
**Summary of Soft Tissue Abnormalities**  
**(Hamsters)**

<b>Group</b>	<b>Material</b>	<b>Dose level mg/kg</b>	<b>Dam</b>	<b>Number of Pups</b>	<b>Description</b>
111	Sham	0.0	S 5333	4	Meningoencephalocele
117	FDA 71-25	3.0	M 5022	1	Meningoencephalocele
118	FDA 71-25	13.0	M 5032	16	Meningoencephalocele

FOOD AND DRUG RESEARCH LABORATORIES, INC.

Groups 111 & 112; 117 through 120

Date August 31, 1972

Species Hamsters

Table 4

Laboratory No. 0895 m

Average Body Weights\*

Group	Material	Dose Level mg/kg	-----Day-----				
			0	6	8	10	14**
111	Sham	0.0	103	108	108	119	140 (20)
112	Aspirin***	250.0	104	105	107	120	140 (21)
117	FDA 71-25	3.0	104	109	112	125	147 (22)
118	FDA 71-25	13.0	101	106	110	122	142 (22)
119	FDA 71-25	60.0	93	100	104	114	132 (21)
120	FDA 71-25	280.0	103	108	111	122	142 (21)

\* Of pregnant dams

\*\* Number of surviving dams in parentheses (c.f. Table 1)

\*\*\* Positive control: 250.0 mg/kg



## Appendix I

### Teratology Study in Hamsters

Virgin adult female golden hamsters from an outbred strain were individually housed in mesh bottom cages in temperature and humidity controlled quarters with free access to food and fresh tap water at all times. They were mated (1 to 1) with mature males and the appearance of motile sperm in the vaginal smear was considered as Day 0 of gestation. Beginning on Day 6 and continuing daily through Day 10 of gestation, the indicated dose levels of the test material were administered by oral intubation; the controls were sham-treated.

Body weights were recorded on Days 0, 8, 10, and 14 of the gestation period. All animals were observed daily for appearance and behavior with particular attention to food consumption in order to better recognize any abnormalities resulting from anorexic effects in the pregnant animal.

On Day 14, all animals were subjected to Caesarian section under deep anesthesia and the numbers of implantation sites, resorption sites, live and dead fetuses were recorded. All live pups were weighed and the genital tract of each dam was examined for any anatomical abnormalities.

All fetuses were examined grossly for the presence of external congenital defects and one-third of each litter underwent detailed visceral examination under 10X magnification. The remaining two-thirds of the pups were cleared in potassium hydroxide, stained with alizarin red dye, and examined for the presence of skeletal abnormalities.

FOOD AND DRUG RESEARCH LABORATORIES, INC.

Group 111

Appendix II

Date August 31, 1972

Material Sham

Reproduction Data in Hamsters (Individual)

Laboratory No. 0895

Dose 0.0 mg/kg

Dam No.	Fate*	Corpora Lutea	Implant Sites	Fetuses		Sex		Resorption Sites	Average Fetus Weight (g)	Remarks
				Alive	Dead	M	F			
S 5331	P	11	10	10		1	9		1.60	
S 5332	P	13	12	10	1	2	8	1	1.15	
S 5333	P	15	16	11	4	1	10	1	1.56	
S 5334	P	5	16					16	----	Died Day 13
S 5335	P	14	11	11		4	7		1.41	
S 5336	NP	10	0						----	
S 5337	P	18	14	14		3	11		1.73	
S 5338	P	16	14	12		3	9	2	1.63	
S 5339	P	17	16	15		7	8	1	1.69	
S 5340	P	9	13		13				----	
S 5341	P	16	15	15		5	10		1.58	
S 5342	NP	7	0						----	
S 5343	P	13	12	12		3	9		1.73	
S 5344	P	11	8	7		2	5	1	2.12	
S 5345	P	12	9	9		5	4		1.77	
S 5346	P	16	13	13		6	7		1.77	
S 5347	P	18	11	11		4	7		1.78	
S 5348	P	13	9	8		4	4	1	1.72	
S 5349	P	13	9	9		4	5		1.80	
S 5350	NP	12	0						----	
S 5351	P	12	11	11		2	9		1.71	
S 5352	P	14	13	13		6	7		1.75	
S 5353	P	16	10	9		3	6	1	2.01	
S 5354	P	17	14	14		5	9		1.66	

\* P = Pregnant; NP = Not Pregnant

FOOD AND DRUG RESEARCH LABORATORIES, INC.

Group 112

Appendix II

Date August 31, 1972

Material Aspirin

Reproduction Data in Hamsters (Individual)

Laboratory No. 0895

Dose 250.0 mg/kg

Dam No.	Fate*	Corpora Lutea	Implant Sites	Fetuses		Sex		Resorption Sites	Average Fetus Weight (g)	Remarks
				Alive	Dead	M	F			
A 5331	P	14	12	2		1	1	10	1.14	
A 5332	P	19	14	14		4	10		1.54	
A 5333	P	17	13	13		6	7		1.48	
A 5334	P	17	13	13		3	10		1.82	
A 5335	P	18	12	11		4	7	1	1.71	
A 5336	P	16	15	15		3	12		1.86	
A 5337	P	19	14	14		5	9		1.51	
A 5338	P	15	10	10		1	9		1.71	
A 5339	P	13	12	12		9	3		1.62	
A 5340	P	15	11	11		6	5		1.56	
A 5341	P	14	12	12		0	12		1.67	
A 5342	P	14	12	12		5	7		1.62	
A 5343	NP	5	0						----	
A 5344	P	16	12	11		3	8	1	1.71	
A 5345	P	18	14	13	1	1	12		1.60	
A 5346	P	14	11	11		2	9		1.77	
A 5347	P	13	10	10		3	7		1.65	
A 5348	P	16	12	12		4	8		1.65	
A 5349	P	17	13	12	1	4	8		1.64	
A 5350	P	13	11	11		4	7		1.78	
A 5351	P	13	12	12		5	7		1.79	
A 5352	P	14	12	12		5	7		1.79	

\* P = Pregnant; NP = Not Pregnant



FOOD AND DRUG RESEARCH LABORATORIES, INC.

Appendix II

Date August 31, 1972

Group 117

Material FDA 71-25

Reproduction Data in Hamsters (Individual)

Laboratory No. 0895 m

Dose 3.0 mg/kg

Dam No.	Fate*	Corpora Lutea	Implant Sites	Fetuses		Sex		Resorption Sites	Average Fetus Weight (g)	Remarks
				Alive	Dead	M	F			
M 5001	P	16	14	14		2	12		1.67	
M 5002	NP	9	0						----	
M 5003	P	16	14	11		6	5	3	1.63	
M 5004	P	16	13	13		5	8		1.94	
M 5005	P	15	11	11		5	6		1.81	
M 5006	P	16	15	15		4	11		1.81	
M 5007	P	16	12	12		5	7		1.75	
M 5008	P	13	10	10		6	4		1.53	
M 5009	P	15	15	14		3	11	1	1.78	
M 5010	NP	7	0						----	
M 5011	P	18	13	13		3	10		1.69	
M 5012	P	16	11	10		3	7	1	1.74	
M 5013	P	16	14	11		2	9	3	1.57	
M 5014	P	16	11	11		5	6		1.86	
M 5015	NP	9	0						----	
M 5016	P	17	12	11		6	5	1	1.79	
M 5017	P	13	12	12		6	6		1.81	
M 5018	P	13	12	11		3	8	1	2.04	
M 5019	P	15	15	14		6	8	1	2.01	
M 5020	P	13	13	11		6	5	2	1.88	
M 5021	P	14	14	12		4	8	2	1.95	
M 5022	P	19	11	10	1	4	6		1.93	
M 5023	P	15	14	14		10	4		1.89	
M 5024	P	15	10	10		3	7		1.90	
M 5025	P	16	14	13		4	9	1	1.81	

\* P = Pregnant; NP = Not Pregnant

FOOD AND DRUG RESEARCH LABORATORIES, INC.

Group 118

Appendix II

Date August 31, 1972

Material FDA 71-25

Reproduction Data in Hamsters (Individual)

Laboratory No. 0895 m

Dose 13.0 mg/kg

Dam No.	Fate*	Corpora Lutea	Implant Sites	Fetuses		Sex		Resorption Sites	Average Fetus Weight (g)	Remarks
				Alive	Dead	M	F			
M 5031	P	17	13	12		3	9	1	1.60	
M 5032	P	17	15	15		2	13		1.28	
M 5033	P	14	10	9		4	5	1	1.92	
M 5034	P	18	14	12		5	7	2	1.71	
M 5035	P	13	9	9		3	6		2.05	
M 5036	P	13	7	7		3	4		2.52	
M 5037	P	19	14	13		7	6	1	1.69	
M 5038	P	13	14	12		4	8	2	1.91	
M 5039	P	15	12	12		5	7		1.71	
M 5040	P	21	17	16		5	11	1	1.64	
M 5041	P	19	17	16		5	11	1	1.64	
M 5042	P	15	13	12		3	9	1	1.74	
M 5043	P	14	11	11		4	7		1.88	
M 5044	P	15	6	5		3	2	1	1.62	
M 5045	P	15	12	10		7	3	2	2.04	
M 5046	P	16	13	12		7	5	1	1.82	
M 5047	P	18	14	13		4	9	1	1.76	
M 5048	P	17	13	12		8	4	1	1.92	
M 5049	P	13	12	11		5	6	1	1.97	
M 5050	P	16	13	12		4	8	1	1.82	
M 5051	P	11	8	8		5	3		2.08	
M 5052	P	14	12	12		2	10		1.56	

\* P = Pregnant; NP = Not Pregnant

FOOD AND DRUG RESEARCH LABORATORIES, INC.

Group 119

Appendix II

Date August 31, 1972

Material FDA 71-25

Reproduction Data in Hamsters (Individual)

Laboratory No. 0895 m

Dose 60.0 mg/kg

Dam No.	Fate*	Corpora Lutea	Implant Sites	Fetuses		Sex		Resorption Sites	Average Fetus Weight (g)	Remarks
				Alive	Dead	M	F			
M 5061	P	14	15	5		2	3	10	2.39	
M 5062	NP	9	0						----	
M 5063	NP	11	0						----	
M 5064	P	11	9	8		5	3	1	1.84	
M 5065	P	13	11		6			5	----	
M 5066	P	13	10	8		3	5	2	1.52	
M 5067	P	13	11	11		3	8		1.70	
M 5068	NP	10	0						----	
M 5069	P	15	10	9		4	5	1	1.59	
M 5070	P	17	14	14		4	10		1.71	
M 5071	P	13	9	8		3	5	1	1.54	
M 5072	P	16	11	11		3	8		1.66	
M 5073	NP	6	0						----	
M 5074	P	24	13	13		7	6		1.89	
M 5075	P	17	14	13		6	7	1	1.71	
M 5076	P	16	14	12		8	4	2	1.62	
M 5077	P	18	12	12		7	5		2.00	
M 5078	P	15	11	11		5	6		1.71	
M 5079	P	13	11	11		7	4		1.92	
M 5080	P	16	14	11		4	7	3	1.89	
M 5081	P	11	7	7		3	4		1.91	
M 5082	P	17	15	14		6	8	1	1.71	
M 5083	P	16	11	11		3	8		1.76	
M 5084	P	15	11	11		6	5		1.72	
M 5085	P	16	12	11	1	4	7		1.81	

\* P = Pregnant; NP = Not Pregnant

FOOD AND DRUG RESEARCH LABORATORIES, INC.

Group 120

Appendix II

Date August 31, 1972

Material FDA 71-25

Reproduction Data in Hamsters (Individual)

Laboratory No. 0895 m

Dose 280.0 mg/kg

Dam No.	Fate*	Corpora Lutea	Implant Sites	Fetuses		Sex		Resorption Sites	Average Fetus Weight (g)	Remarks
				Alive	Dead	M	F			
M 5091	P	13	11	9		4	5	2	1.83	
M 5092	P	11	9	1		1	0	8	2.57	
M 5093	P	14	13	13		5	8		1.67	
M 5094	P	20	16	15		6	9	1	1.65	
M 5095	P	16	12	12		6	6		1.61	
M 5096	P	15	7	7		2	5		2.65	
M 5097	P	15	12	12		3	9		1.90	
M 5098	P	16	15	14		9	5	1	1.91	
M 5099	NP	8	0						----	
M 5100	P	18	13	13		2	11		1.77	
M 5101	P	13	12	12		3	9		1.74	
M 5102	P	15	10	10		6	4		1.89	
M 5103	P	14	8	1		0	1	7	1.50	
M 5104	P	14	11	10		5	5	1	1.90	
M 5105	P	18	15	14		5	9	1	1.98	
M 5106	P	15	13	13		6	7		1.92	
M 5107	P	16	15	15		6	9		1.77	
M 5108	P	16	13	12		6	6	1	1.76	
M 5109	P	15	10	9		3	6	1	1.97	
M 5110	P	17	13	10	1	3	7	2	1.60	
M 5111	P	16	11	11		6	5		1.79	
M 5112	P	13	11	10		3	7	1	1.85	

\* P = Pregnant; NP = Not Pregnant

RABBITS

**F**ood and **D**rug **R**esearch **L**aboratories  
I N C O R P O R A T E D



Maurice Avenue at 58<sup>th</sup> Street  
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**F I N A L**  
**R E P O R T**

Submitted to: DHEW/Public Health Service  
Food and Drug Administration CA-272  
5600 Fishers Lane-Room 5C-13  
Rockville, Maryland 20852

Date October 2, 1972

Laboratory No. 0896 m  
Contract No. FDA 71-260

Sample: White crystalline material

Marking: FDA 71-25 (Butylated hydroxy toluene (Ionol))

Examination Requested: Teratologic evaluation of FDA 71-25 in rabbits

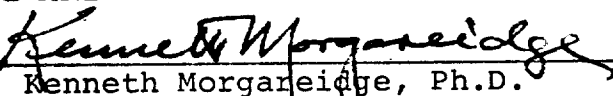
Procedure: (See Appendix I)

Results: (To Follow)

Conclusion:

(This test has been deferred due to unavailability of suitable rabbits.)

FOOD AND DRUG RESEARCH LABORATORIES, INC.

  
Kenneth Morgareidge, Ph.D.  
Vice President

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## Appendix I

### Teratology Study in Rabbits

Virgin, adult, Dutch-belted female rabbits were individually housed in mesh bottom cages in temperature and humidity-controlled quarters with free access to food and fresh tap water. On Day 0, each doe was given an injection of 0.4 ml of human chorionic gonadotropin (400 IU) via the marginal ear vein. Three hours later, each doe was inseminated artificially with 0.3 ml of diluted semen from a proven donor buck using approximately  $20 \times 10^6$  motile sperm according to the procedure described by Vogin et al (Pharmacologist 11, 282 (1969)). Beginning on Day 6 and continuing daily through Day 18 the females were dosed with the indicated dosages by oral intubation; the controls were sham treated.

Body weights were recorded on Days 0, 6, 12, 18, and 29 of gestation. All animals were observed daily for appearance and behavior, with particular attention to food consumption and body weight in order to rule out any abnormalities which may have occurred as a result of anorexic effects in the pregnant female animal.

On Day 29 all does were subjected to Caesarean section under surgical anesthesia, and the numbers of corpora lutea, implantation sites, resorption sites and live and dead fetuses were recorded. Body weights of the live pups were also recorded. The urogenital tract of each animal was examined in detail for normality. In addition all fetuses underwent a detailed gross examination for the presence of external congenital abnormalities. The live fetuses of



each litter were then placed in an incubator for 24 hours for the evaluation of neonatal survival. All surviving pups were sacrificed, and all pups examined for visceral abnormalities (by dissection). All fetuses were then cleared in potassium hydroxide (KOH), stained with alizarin red S dye and examined for skeletal defects.